Kidney International, Vol. 60 (2001), pp. 228–234

Long-term beneficial effect of ACE inhibition on diabetic nephropathy in normotensive type 1 diabetic patients

HANS-HENRIK PARVING, EVA HOMMEL, BERIT RUUD JENSEN, and HENRIK POST HANSEN

Steno Diabetes Center, Copenhagen, Denmark

Long-term beneficial effect of ACE inhibition on diabetic nephropathy in normotensive type 1 diabetic patients.

Background. The purpose of this study was to assess whether long-term (8 years) inhibition of angiotensin-converting enzyme (ACE) protects kidney function in normotensive type 1 diabetic patients with diabetic nephropathy.

Methods. We performed an open randomized follow-up study of normotensive type 1 diabetics with nephropathy either treated ($N = 15$) or not ($N = 17$) with captopril twice per day (average 74, range 12.5 to 125 mg/day). The main outcome measures were arterial blood pressure, albuminuria, and glomerular filtration rate (GFR; ^{51}Cr-EDTA plasma clearance, twice yearly).

Results. Arterial blood pressure (mm Hg) was kept constant in the captopril group, at baseline (mean, SEM), 128/78 (3/2) and during follow-up 129/77 (4/1) but increased significantly in the control group from 127/79 (2/1) to 137/84 (5/2) ($P < 0.01$). Furthermore, 8 out of the 17 control subjects required treatment with blood pressure-lowering drugs because they developed hypertension. The fractional albumin clearance ($\times 10^{-5}$) remained unchanged in the captopril group: baseline [10.8 (1.25) geometric mean and antilog (SEM)] during the eight years [11.8 (1.47)], while a significant rise occurred in control patients: 13.3 (1.23) to 26.2 (1.42) ($P < 0.05$). Baseline GFR was nearly identical: 111 (6) and 115 (4) mL/min/1.73 m^2 in the captopril and control group, respectively. The median (range) rate of decline in GFR (mL/min/year) was 1.7 (10.7 to −2.0) in the captopril group versus 2.8 (17.7 to −2.6) in the control group (P = NS).

Conclusions. The beneficial effect of captopril in arresting the rise in systemic blood pressure and albuminuria is long lasting. A loss in GFR is minimal in most patients with diabetic nephropathy if normotension is sustained by prospective treatment with ACE inhibitors or restored by implementation of other antihypertensive medications with the development of hypertension.

Key words: albuminuria, kidney function, arterial blood pressure, end-stage renal disease, glomerular filtration rate, hypertension, renoprotection.

Received for publication March 28, 2000
and in revised form January 18, 2001
Accepted for publication January 24, 2001

The clinical syndrome of diabetic nephropathy is characterized by a progressive rise in albuminuria and arterial blood pressure (BP) associated with a relentless decline in glomerular filtration rate (GFR) of approximately 10 to 14 mL/min/year [1]. Even though arterial hypertension is an early and frequent phenomenon [2, 3], normotension is present in approximately 25% of the cases when kidney function is well preserved [2, 3]. Previous studies have clearly documented that BP elevation and albuminuria are powerful progression promoters, as reviewed by Rossing [4]. In complete agreement herewith, antihypertensive treatment has been shown to reduce albuminuria and postpone end-stage renal disease (ESRD) in hypertensive type 1 diabetic patients with persistent albuminuria [5]. Information is lacking on treatment modalities, including BP-lowering agents with a beneficial effect on kidney function in normotensive type 1 diabetic patients with diabetic nephropathy. In contrast, studies in normotensive streptozotocin diabetic rats have demonstrated that angiotensin-converting enzyme (ACE) inhibition initiated at diabetes onset confers long-term protection against the development of diabetic glomerulopathy (primary prevention) [6]. Long-term ACE inhibition and treatment with calcium channel blockers can delay the development of diabetic nephropathy in normotensive type 1 diabetic patients with persistent microalbuminuria (secondary prevention) [7]. Recently, our group has shown that the beneficial effect of ACE inhibition in the prevention of diabetic nephropathy in type 1 diabetic patients is long lasting and is associated with the preservation of normal GFR [8].

We assessed whether long-term (8 years) inhibition of ACE protects kidney function in normotensive type 1 diabetic patients with diabetic nephropathy. The impact of a two-month treatment pause on albuminuria and GFR was also investigated. An interim report after one year of study has previously been published [9].

METHODS

We examined the records of all type 1 diabetic patients ($N = 180$) with albuminuria >300 mg/24 h (200 μg/min)

Table 1. Clinical and laboratory data at baseline in normotensive type 1 diabetic patients with diabetic nephropathy

Parameter	Captopril-treated group	Control
Number and sex	5 F, 10 M	4 F, 13 M
Age *years*	32 (8)	30 (8)
Duration of diabetes *years*	20 (8)	20 (8)
N with simplex/proliferative retinopathy	10/5	9/8
Vibratory perception threshold *volts*	15 (8)	21 (16)
Hemoglobin A_{1c} %	9.5 (1.6)	8.7 (0.8)
Insulin dose *U/kg/24 h*	0.66 (0.20)	0.64 (0.20)
Protein intake *g/24 h*	77 (27)	80 (23)
Urinary sodium excretion *mmol/min*	0.16 (0.02)	0.15 (0.02)
Body mass index kg/m^2	22.2 (2.3)	22.9 (1.6)

Values are means (SD).

who visited the outpatient clinic at Hvidöre Hospital in 1985. One hundred seven patients with arterial hypertension (>160/95 mm Hg; World Health Organization criteria) were excluded from further investigation. The remaining patients ($N = 73$) were invited to participate if they fulfilled the following criteria: persistent albuminuria (>300 mg/24 h), serum creatinine concentration <120 μmol/L, or a GFR >60 mL/min/1.73 m^2, average of three or more consecutive BP readings below 150/90 mm Hg, no edema, not taking other drugs apart from oral contraceptives, age of less than 50 years, and onset of diabetes before the age of 41. Thirty-five patients (19%) fulfilled these criteria, of whom two men refused the trial; the remaining 33 patients gave fully informed consent. The study was approved by the scientific ethics committee of Copenhagen County (Table 1).

The patients were matched in pairs according to albuminuria, arterial BP, and GFR levels, and were randomized (concealed) either to receive captopril ($N = 16$) or not to receive hypotensive treatment (controls; $N = 17$). One woman with persistent microscopic hematuria, both before and during the first eight months of treatment with captopril, was excluded from the study and from the statistical analysis because the kidney biopsy showed mesangioproliferative glomerulonephritis superimposed on diffuse diabetic glomerulosclerosis. This left 15 patients in the captopril group. Treatment with captopril was aimed primarily at preventing the rise in arterial BP that occurs in diabetic nephropathy and secondarily at reducing the mean arterial BP by 5 mm Hg. Initially, all treated patients received 12.5 mg captopril before breakfast and dinner. The dose was adjusted at the visits to the outpatient clinic (once per month until the third month, and once every 3 months thereafter). The captopril-treated group received captopril b.i.d., with an average of 74 mg/day (12.5 to 125 mg/day) at the eight-year follow-up. Eight out of the 17 control patients started treatment with BP-lowering drugs during the investigation period (diuretics, dihydropyridine calcium antagonist, and β blocker). Treatment was initiated because of arterial BP elevation (>160/95 mm Hg) with ($N = 3$) or without ($N = 5$) edema formation. All patients had been insulin dependent from the time of diagnosis, and all were at least receiving two daily injections of highly purified porcine insulin. All patients were on their usual diabetic diet without sodium or protein restriction. Diabetic nephropathy was diagnosed clinically on the basis of persistent albuminuria (>300 mg per 24 h), presence of diabetic retinopathies, and the absence of any clinical or laboratory evidence of other kidney or renal tract disease [10].

The investigation in each patient was carried out between 8:00 a.m. and 1:30 p.m. The patients had their usual breakfast and morning insulin. The patients were supine during the entire investigation except when urinating. The patients drank 200 mL tap water per hour during the procedures. The clearance studies were carried out every six months. GFR was measured after a single intravenous injection of 3.7 MBq chromium-51–labeled edetic by studying its disappearance in plasma over four hours [11]. The mean intra-individual coefficient of variation of GFR from day to day was 4.0% in our laboratory. Albuminuria was measured during the four-hour clearance period by radioimmunoassay in all urine samples to 1992. The assay has a sensitivity of 0.5 mg/L and a coefficient of variation of 9% [12]. After 1992, an enzyme-linked immunosorbent assay (ELISA) method was used with a sensitivity of 0.01 mg/L and a coefficient of variation of 8.3% [13]. The correlation between the two methods was $r = 0.99$. Fractional clearance of albumin was obtained by dividing the clearance of albumin (calculated as UV/P, where U is urine albumin concentration, V is urine flow, and P is plasma albumin concentration) by the simultaneous measured GFR. BP was measured with Hawksley random zero device (cuff size 25 × 12 cm) on the right arm. Two readings were taken at the beginning, middle, and end of each clearance period. Two readings were also taken when the patients visited the outpatient clinic between 2:00 and 4:00 p.m. Diastolic BP was recorded at the point of disappearance of the Korotkoff sounds (phase V). Mean BP was calculated as the diastolic BP plus one third of the pulse amplitude.

Blood glucose concentration was measured hourly during the four-hour clearance period by reflectance meter (Reflomat; Boehringer Mannheim, Ingelheim, Germany). Leukocyte counts and measurement of serum electrolyte, albumin, hemoglobin, and cholesterol concentrations during each investigation were carried out by conventional laboratory techniques. Stable hemoglobin A_{1c} was measured before and at each investigation (normal range of 4.1 to 6.1% of total hemoglobin). Twenty-four–hour urine collections were used for calculating

Table 2. Effects of captopril on arterial blood pressure, albuminuria, rate of decline in glomerular filtration rate (GFR) in normotensive type 1 diabetic patients with diabetic nephropathy during 8 years of follow-up

	Captopril ($N = 15$)		Control ($N = 17$)	
	Baseline	During 8 years follow-up	Baseline	During 8 years follow-up
Arterial blood pressure *mm Hg*	128/78 (3/2)	129/77 (4/1)	127/79 (2/1)	137/84 (5/2)[b]
Albuminuria[a] *mg/24 h*	838 (x/−1.15)	657 (x/−1.29)	1140 (x/−1.16)	1379[b] (x/−1.17)
GFR *mL/min/1.73 m²*	111 (6)	98 (8)[c]	115 (4)	97 (6)[c]
ΔGFR[d] *mL/min/year*		1.7 (10.7 to −2.0)		2.8 (17.7 to −2.6)

Values are means (SE).
[a] Geometric mean (x/−antilog SE)
[b] $P < 0.02$, comparison between captopril and control means during the entire 8-year follow-up period
[c] Values at end of follow-up
[d] Median (range)

protein intake from the urinary urea nitrogen and an estimated nonurea nitrogen excretion of 31 mg/kg/day. Given a constant nitrogen balance, nitrogen intake equals urinary urea nitrogen excretion and nonurea nitrogen excretion, protein intake (g/day) = nitrogen × 6.25.

After eight years, 10 out of the 15 captopril-treated patients and 4 out of 8 control patients receiving non-ACE inhibition antihypertensive drugs from the control group were subsequently investigated after a BP-lowering treatment pause of two months (Table 3). The reasons for not conducting this investigation in the remaining five patients in the captopril-treated group were dead in bed ($N = 1$), hemodialysis ($N = 1$), emigration ($N = 1$), combined diabetic glomerulosclerosis and glomerulonephritis ($N = 1$), and intercurrent illness ($N = 1$). The reasons in the four control patients included ESRD ($N = 3$) and stroke ($N = 1$). BP, albuminuria, and GFR were measured using the previously mentioned methods.

Statistical analysis

An intention-to-treat strategy in the statistical analysis was applied since all patients (captopril, $N = 15$, and control, $N = 17$) who completed the first 12 months of the study period were included. Variables measured during the trial for each patient ($N = 32$) are summarized by one mean variable of all measurements over the entire treatment period for that patient. Descriptive information is expressed as means and SD, and results are expressed as mean and SE. Albuminuria and fractional albumin clearance are given as geometric mean x/− antilog SE due to their positively skewed distribution. The paired and unpaired Student *t* tests were used, and a *P* value of <0.05 (two tailed) considered significant. The rate of deterioration of renal function was analyzed by regression lines for ^{51}Cr-EDTA clearance over time, determined for each patient over the entire study period. Linear regression and stepwise linear regression analysis were used to evaluate the correlation between putative predictors (albuminuria, BP, hemoglobin A_{1c}, baseline GFR, urinary sodium excretion, dietary protein intake, and age) and rate of decline in GFR. All calculations were made with a commercially available program Statgraphic (STSC, Rockville, MD, USA).

RESULTS

The two groups were well matched at baseline (Tables 1 and 2). The average captopril dose was 74 (12.5 to 125) mg/daily given two times per day during follow-up. Five out of 17 patients in the control group developed arterial hypertension (repeated recording >160/95 mm Hg) and were treated with diuretics ($N = 3$), dihydropyridine calcium antagonist ($N = 3$), and β-blockers ($N = 1$). In addition, three patients in the control group developed edema and BP elevation requiring treatment with diuretics. In total, 8 out of 17 control patients received BP-lowering drugs.

The median initial decline in GFR (mL/min) during the first six months of the study was 8 (12.9 to −1.1) and 2 (9.9 to −0.6) in the captopril-treated group compared with the control group (P = NS).

The average values and the course of arterial BP, GFR, and fractional albumin clearance are shown in Table 2 and Figure 1. A comparison between the mean value of arterial BP and geometric valve of albuminuria revealed significantly lower values of both variables in the captopril-treated group as compared with the control group ($P < 0.05$). Figure 1 shows that the separation between these two variables occurs right from the start of captopril treatment. The rate of decline in GFR was 1.7 (10.7 to −2.0) mL/min/year and 2.8 (17.7 to −2.6) mL/min/year in the captopril-treated versus the control group, respectively (P = NS).

In univariate analyses, no significant correlation was found between the rate of decline in GFR during the study and the following baseline variables: albuminuria, hemoglobin A_{1c}, systolic and diastolic BP, urinary sodium excretion, dietary protein intake, and the age of the patient. During follow-up period, a significant univariate correlation between the rate of decline in GFR and albu-

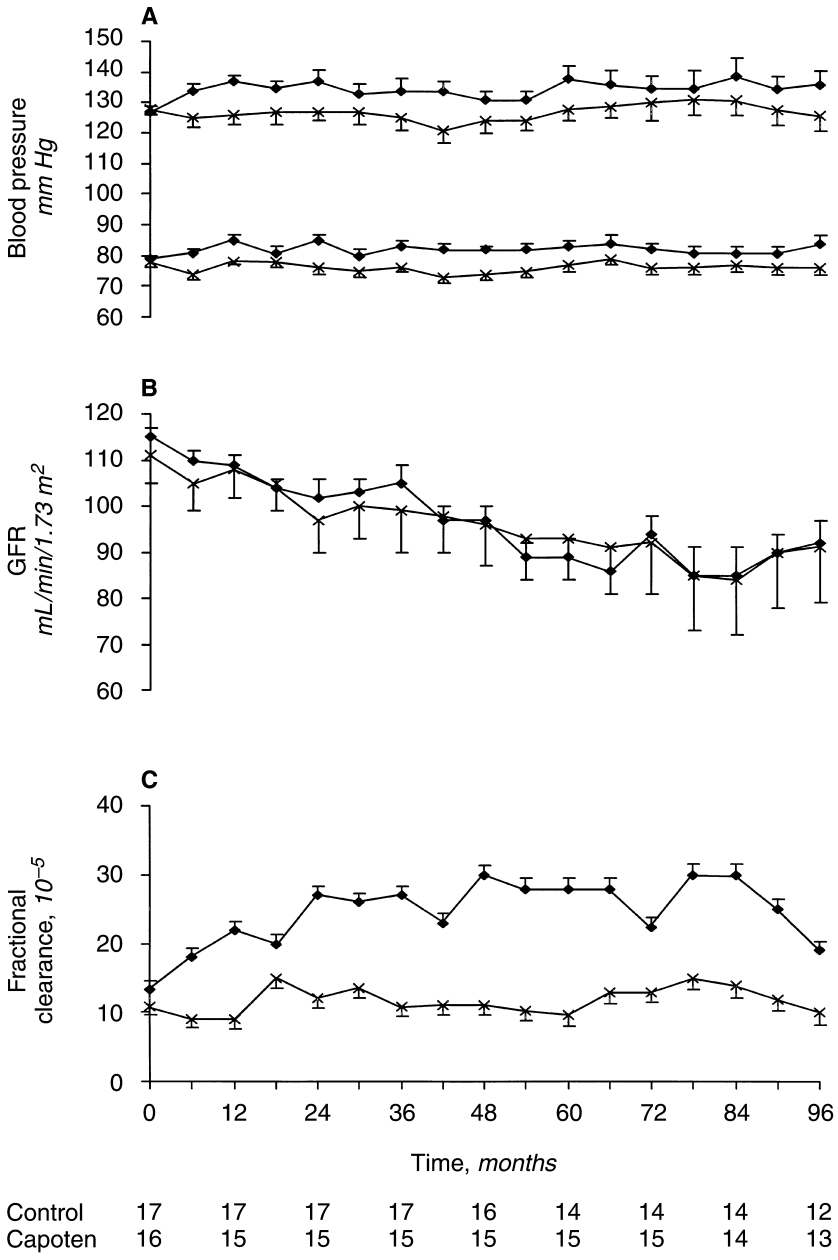

Fig. 1. (*A–C*) Average course of systemic blood pressure (BP), glomerular filtration rate (GFR), and fractional albumin clearance is shown in type 1 diabetic patients with nephropathy treated with angiotensin-converting enzyme (ACE) inhibition (×) or not (control group; ◆). Eight out of 17 control patients required treatment with BP-lowering drugs because arterial BP elevation >160/95 mm Hg. Systemic BP and fractional albumin clearance were both significantly lower than the control group ($P < 0.05$).

minuria and systolic and diastolic BP were demonstrated ($P < 0.05$), while the remaining variables mentioned previously in this article showed no significant correlation. In a multivariate model, high values of albuminuria and systolic BP during the observation period were associated with enhanced decline in GFR, independently of the randomized group (adjusted $R^2 = 0.60$).

The huge variability in the individual rate of decline in GFR is depicted in Figure 2. The five patients with a rate of decline in GFR >10 mL/min/year had significantly higher albuminuria and total cholesterol ($P < 0.05$), while other putative progression promoters such as BP, hemoglobin A_{1c}, and protein intake did not differ between fast and slow progressors. One patient died in each group, but three control patients developed ESRD, requiring dialysis or transplantation.

Four men (one treated with captopril) had a sudden onset of nephrotic-range albuminuria. Consequently, a kidney biopsy was performed revealing only diffuse diabetic glomerulopathy in three patients, while the last patient (control) had combined diabetic glomerulopathy and glomerulonephritis. Asymptomatic microscopic hematuria was present in that patient. This patient was excluded from further follow-up at three years, but was included in the intervention-to-treat analysis.

Even though it was only possible to evaluate the two-

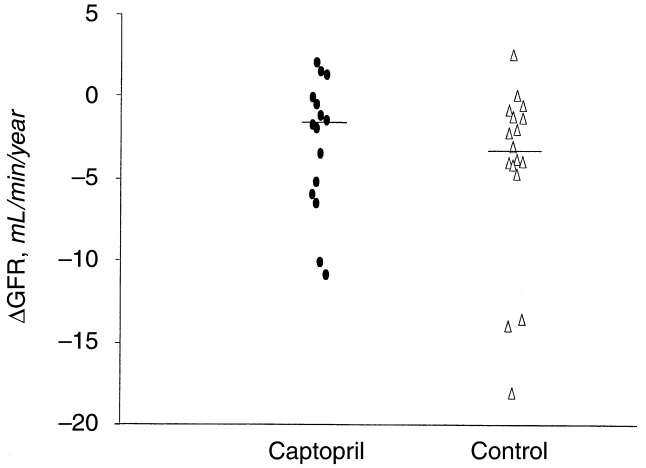

Fig. 2. Individual course of glomerular filtration rate (GFR) is depicted in type 1 diabetic patients with nephropathy treated with angiotensin-converting enzyme (ACE) inhibition (●) or belonging to the control group (△). Eight out of 17 control patients required treatment with BP-lowering drugs because arterial BP elevation >160/95 mm Hg. Systemic BP and fractional albumin clearance were both significantly lower than the control group ($P < 0.05$).

month off-treatment effect in a limited number of patients, as previously explained in detail, a significant elevation in arterial BP, albuminuria, and GFR was clearly documented (Table 3). Albuminuria was more than doubled, and GFR rose 9 mL/min, which was nearly equivalent to the initial GFR drop of 8 mL/min induced by ACE inhibition.

Hemoglobin A_{1c}, serum concentration of albumin, cholesterol, sodium, potassium, and urinary sodium excretion and protein intake showed no significant changes during the study within or between the two groups (data not shown). Five captopril-treated and six control patients developed proliferative retinopathy during the eight years of study. No severe side-effects, including hyperkalemia, occurred, and all patients continued or started ACE inhibition after termination of the trial.

DISCUSSION

Our long-term prospective randomized controlled trial in normotensive type 1 diabetic patients with diabetic nephropathy indicates that ACE inhibition can arrest the rise in systemic BP and albuminuria. Furthermore, a loss in GFR is minimal in most but not all patients with diabetic nephropathy if normotension is sustained. However, our study did not reveal any significant difference in the rate of GFR decline between the two groups, which in part may reflect the relative small number of subjects studied. Furthermore, the renoprotective effect of ACE inhibition is underestimated because of a reversible hemodynamic impairment of GFR that does not attenuate over time. The initial drop in GFR induced by ACE inhibition was completely regained after two months off of the ACE inhibition treatment. One-half of the control patients developed arterial hypertension requiring treatment with BP-lowering drugs (non-ACE inhibitors). Finally, short-term withdrawal (two months) of long-term BP-lowering treatment (eight years) induced a significant rise in arterial BP, albuminuria, and GFR.

The natural course of diabetic nephropathy is characterized by a progressive rise in albuminuria and arterial BP associated with a relentless decline in GFR of approximately 10 to 14 mL/min/year [1]. This information was generated from studies not applying antihypertensive treatment. The rise in albuminuria and BP was much less in our study than observed in the previously mentioned studies, but half of our control ("untreated") patients received antihypertensive treatment because they developed hypertension. It is well documented that BP-lowering drugs reduce BP, diminish albuminuria, and slow down the rate of decline in GFR [1, 3, 5, 10, 14].

It is well documented that elevated BP and albuminuria are major risk factors for losing filtration power [4]; conversely, aggressive antihypertensive treatment reduces albuminuria and the rate of decline in GFR, which postpones ESRD and prolongs survival in type 1 diabetic patients with nephropathy [1, 5]. Renoprotection, a beneficial effect on kidney function and structure above and beyond that expected from the BP-lowering effect alone, has been demonstrated using ACE inhibition in diabetic and nondiabetic nephropathies [3, 5, 14]. The validity of this concept in normotensive diabetic patients has not been proven since the majority of the patients enrolled in the previously mentioned trials were hypertensive. The Captopril Collaborative Study is an exception, since approximately 100 normotensive type 1 diabetic patients with diabetic nephropathy participated for three years [3]. Unfortunately, no specific information on this important subgroup has been reported. Because of its limited power, our study does not allow for any conclusion regarding a specific renoprotective effect of ACE inhibition. Since the worsening in GFR is a rather slow process (low-risk patient group), the number of patients that must be enrolled in a trial aimed at elucidating a specific renoprotective effect must be very large, probably more than a thousand.

Even though the progression in kidney function in general was slow in our patients, the condition was not benign since four patients (one treated with captopril) had a sudden onset of nephrotic-range albuminuria; five patients (2 on captopril therapy) had a rate of decline in GFR above 10 mL/min/year, and three control patients developed ESRD. Albuminuria and systolic BP acted as progression promoters.

The reduction in albuminuria could not be explained by the small changes in GFR or serum albumin since a parallel change in fractional albumin clearance occurred.

Table 3. Subgroup analysis: Changes in mean arterial BP (MABP), glomerular filtration rate (GFR), and albuminuria before and after 2 months withdrawal of antihypertensive treatment (ACE inhibition vs. non-ACE inhibition) in 14 normotensive type 1 diabetic patients with diabetic nephropathy

	MABP[a] *mm Hg*			GFR[a] *mL/min/1.73 m²*			Albuminuria[b] *mg/24 h*		
	8 years	8 years + 2 months	Δ[d]	8 years	8 years + 2 months	Δ[d]	8 years	8 years + 2 months	Δ[c]
Captopril ($N = 10$)	88 (8)	92 (10)	+5 (0 to 9)[e]	94 (40)	103 (36)	+9 (1 to 17)[e]	227 (2)	541 (1)	138 (52 to 271)[f]
Control ($N = 4$)	97 (10)	106 (11)	+9 (5 to 13)[f]	89 (8)	100 (9)	+12 (6 to 17)[f]	935 (2)	1618 (2)	73 (−16 to 255)
All ($N = 14$)	90 (10)	96 (12)	+6 (3 to 9)[f]	92 (34)	102 (30)	+10 (4 to 15)[f]	340 (1)	739 (1)	117 (55–204)[f]

[a] Mean (SEM)
[b] Geometric mean (antilog SEM)
[c] Average relative change (%) from visit 8 years to +2 months (95% confidence interval)
[d] Average absolute change from visit 8 years
[e] $P < 0.05$ difference between 8 years and 8 years + 2 months
[f] $P < 0.01$ difference between 8 years and 8 years + 2 months

Previous studies suggest that the antiproteinuric effect of ACE inhibition is due to diminished glomerular capillary hydraulic pressure and/or enhanced intrinsic selectivity of the glomerular capillary wall [6, 15]. Recently, Imanishi et al estimated a reduction in glomerular hydraulic capillary pressure during ACE inhibition in human diabetes [16]. A major part of the antiproteinuric effect must be functional since it is present shortly after initiation of ACE inhibition and disappears after a short pause in treatment.

De Jong, Navis, and De Zeeuw have recently highlighted evidence suggesting that proteinuria should be reduced as far as possible in diabetic and nondiabetic nephropathies [17]. First, a reduction in proteinuria when patients start antihypertensive treatment predicts the efficacy of subsequent renoprotection: The greater the reduction, the better the efficacy [18–20]. Second, the residual proteinuria during treatment with antihypertensive drugs is proportional to the rate of decline in GFR, as also demonstrated in our study [4]. We suggest that elimination of residual proteinuria thus may be of prime importance and a novel target in renoprotection.

The second part of our study carried out eight years after start of the trial and after two months of withdrawal of the BP-lowering therapy showed a return toward the GFR values before treatment (baseline). The initial fall in GFR in the intervention group must therefore be regarded as a reversible hemodynamic phenomenon. Consequently, the renoprotective effect of ACE inhibition is underestimated. Similar findings have been demonstrated in normotensive type 1 diabetic patients with microalbuminuria [8] and hypertensive type 1 diabetic patients with diabetic nephropathy [21]. A comparison of time-to-event (for example, ESRD) and GFR slope-based analysis in nephrology clinical trials has revealed that time-to-event is more powerful if the initial acute effects of intervention on GFR are large and mean GFR progression is slow [22].

Our study has several limitations. First, it is not blinded, and second, because of the few study subjects it lacks sufficient statistical power to detect the small observed differences in the rate of decline in GFR. Finally, there is an incomplete evaluation of the withdrawal of BP-lowering treatment.

In conclusion, the beneficial effect of ACE inhibition in arresting the rise in systemic BP and albuminuria is long lasting. A loss of GFR is minimal in most patients with diabetic nephropathy if normotension is sustained by prospective treatment with ACE inhibitors or is restored by implementation of other antihypertensive medications with the development of hypertension. The renoprotective effect of ACE inhibition is underestimated due to a reversible hemodynamic impairment of GFR that does not attenuate over time.

Reprint requests to Hans-Henrik Parving, M.D., D.M.Sc., Steno Diabetes Center, Niels Steensens Vej 2, DK-2820 Gentofte, Denmark.
E-mail: hhp@novo.dk

REFERENCES

1. Parving H, Østerby R, Ritz E: Diabetic nephropathy, in *The Kidney*, edited by Brenner BM, Levine S, Philadelphia, W.B. Saunders, 2000, pp 731–1773
2. Parving H-H, Hommel E, Mathiesen ER, *et al:* Prevalence of microalbuminuria, arterial hypertension, retinopathy and neuropathy in patients with insulin-dependent diabetes. *Br Med J* 296:156–160, 1988
3. Lewis E, Hunsicker L, Bain R, Rhode R: The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. *N Engl J Med* 329:1456–1462, 1993
4. Rossing P: Promotion, prediction, and prevention of progression in diabetic nephropathy. *Diabet Med* 15:900–919, 1998
5. Parving H-H: Renoprotection in diabetes: Genetic and non-genetic risk factors and treatment. *Diabetologia* 41:745–759, 1998
6. Zatz R, Dunn BR, Meyer TW, *et al:* Prevention of diabetic glomerulopathy by pharmacological amelioration of glomerular capillary hypertension. *J Clin Invest* 77:1925–1930, 1986
7. Crepaldi G, Carta Q, Deferrari G, *et al:* Effects of lisinopril and nifedipine on the progression of overt albuminuria in IDDM patients with incipient nephropathy and normal blood pressure. *Diabetes Care* 21:104–110, 1998
8. Mathiesen ER, Hommel E, Hansen HP, *et al:* Randomised controlled trial of long term efficacy of captopril on preservation of kidney function in normotensive patients with insulin dependent diabetes and microalbuminuria. *Br Med J* 319:24–25, 1999
9. Parving H-H, Hommel E, Nielsen MD, Giese J: Effect of captopril

on blood pressure and kidney function in normotensive insulin dependent diabetics with nephropathy. *Br Med J* 299:533–536, 1989
10. Parving H-H, Andersen AR, Smidt UM, Svendsen PA: Early aggressive antihypertensive treatment reduces rate of decline in kidney function in diabetic nephropathy. *Lancet* 1:1175–1179, 1983
11. Bröchner-Mortensen J, Giese J, Rossing N: Renal inulin clearance versus total plasma clearance of ^{51}Cr-EDTA. *Scand J Clin Lab Invest* 23:301–305, 1969
12. Miles DW, Mogensen CE, Gundersen HJG: Radioimmunoassay for urinary albumin using a single antibody. *Scand J Clin Lab Invest* 26:5–11, 1970
13. Jensen T, Deckert M, Dawnay A, Feldt-Rasmussen B: Micro-ELISA for the quantitation of human urinary and serum retinol-binding protein. *Diabetes Res* 10:93–95, 1989
14. Björck S, Mulec H, Johnsen SA, *et al:* Renal protective effect of enalapril in diabetic nephropathy. *Br Med J* 304:339–343, 1992
15. Morelli E, Loon N, Meyer TW, *et al:* Effects of converting-enzyme inhibition on barrier function in diabetic glomerulopathy. *Diabetes* 39:76–82, 1990
16. Imanishi M, Yoshioka K, Konishi Y, *et al:* Glomerular hypertension as one cause of albuminuria in type II diabetic patients. *Diabetologia* 42:999–1005, 1999
17. de Jong PE, Navis GJ, De Zeeuw D: Renoprotective therapy: Titration against urinary protein excretion. *Lancet* 354:352–353, 1999
18. Rossing P, Hommel E, Smidt UM, Parving H-H: Reduction in albuminuria predicts a beneficial effect on diminishing the progression of human diabetic nephropathy during antihypertensive treatment. *Diabetologia* 37:511–516, 1994
19. Rossing P, Hommel E, Smidt UM, Parving H-H: Reduction in albuminuria predicts diminished progression in diabetic nephropathy. *Kidney Int* 45(Suppl 45):S145–S149, 1994
20. Apperloo AJ, De Zeeuw D, De Jong PE: A short-term antihypertensive treatment-induced fall in glomerular filtration rate predicts long-term stability of renal function. *Kidney Int* 51:793–797, 1997
21. Hansen HP, Rossing P, Tarnow L, *et al:* Increased glomerular filtration rate after withdrawal of long-term antihypertensive treatment in diabetic nephropathy. *Kidney Int* 47:1726–1731, 1995
22. Greene T, Lau J, Levey AS: Interpretation of clinical studies of renal disease, in *Immunological Renal Diseases*, edited by Neilson EG, Couser WG, Philadelphia, Lippincott-Raven, 1997, pp 887–911